

## 1. THE INVENTION

The present invention relates to methods and compositions for stimulating liver regeneration in subjects with liver disorders. The methods and compositions of the invention provide for the transplantation of bone marrow cells into a transplant recipient to result in the production of hepatocytes, bile ductal cells as well as oval cells during liver regeneration. The invention also provides a method for deriving enriched populations of hepatic oval cells, considered to be hepatic stem cells, using antibodies that recognize the Thy-1 cell surface antigen expressed on the surface of hepatic oval cells.

## 2. THE CLAIMED INVENTION IS NOVEL

Claims 20-21 are alleged to lack novelty under PCT Article 33(2) as being anticipated by Petersen et al., (FASEB J. 12:A468, 1998: "Petersen I") or Peterson et al. Hepatology 27:433-445; "Petersen II") or Craig (J. Exp. Med. 177:1331-13342, 1993; "Craig"). The Authorized Officer maintains that the Peterson references teach a method for isolating a highly enriched population of hepatic oval cells expressing the hematopoietic stem cell marker Thy-1 using flow cytometry coupled with the use of a Thy-1 antibody. The Examiner further maintains that Craig discloses a method for isolating human hematopoietic cells expressing Thy-1 from human fetal liver using flow cytometry coupled with the use of a novel Thy-1 antibody. Claims 20-21 are not anticipated by the cited references for reasons detailed below.

First, the Peterson references cited by the Authorized Officer were references published by the inventor within one year of the February 26, 1999 effective filing date. Thus, Applicants can successfully antedate the cited references upon submission of a Katz type Declaration.

Second, the Craig reference merely describes the expression of Thy-1 on the surface of hematopoietic progenitor cells. Craig fails to disclose the expression of Thy-1 on the surface of hepatic oval cells, *i.e.*, cells that were also shown to express alpha-fetoprotein (AFP), gamma-glutamyl transpeptidase (GGT), cytokeratin 19 (CK-19), OC.2 and OV-6, all known markers for oval cell identification. In view of the differences between the Craig reference and the invention encompassed by claims 20 and 21, *i.e.*, a method for enriching for hepatic oval cells, the claimed invention cannot be anticipated.

### 3. THE CLAIMED INVENTION IS INVENTIVE

Claims 22-24 are alleged to lack an inventive step under PCT Article 33(3) as being obvious over the Peterson references or Craig in view of Reid.

As indicated above, the Peterson references cannot be used as prior art against the present invention because the references were published by the inventor within one year of the February 26, 1999 effective filing date.

As indicated above the Craig reference merely discloses the expression of Thy-1 on the surface of hematopoietic progenitor cells. Additionally, Reid only discloses a composition comprising a cell culture of immature animal cells which may

differentiate into mature hepatocytes. Neither Craig nor Reid, individually or in combination, teach or even suggest a composition comprising an enriched population of oval cells.

**3. THE CLAIMS ARE FULLY SUPPORTED BY THE  
DESCRIPTION OF THE INVENTION**

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention.

The test for enablement is whether one reasonably skilled in the art could make or use the invention without undue experimentation from the disclosure in the patent coupled with what is known in the art at the time the patent was filed.

The instant specification as filed discloses methods for obtaining bone marrow (see p.10, lines 22 through p.11, line 10 of the specification); methods for enriching for stem cells (see p.11, line 11 through p.17, line 4 of the specification) and/or enriching for hepatic oval cells (see p.13, line 6 through p.15, line 26 of the specification); and methods for administering stem cells and/or oval cells to a subject in need of transplantation (p.15, line 29 through p. 17, line 13 of the specification). In addition, it should be noted that techniques for bone marrow transplantation are well known in the art as bone marrow transplantation has been used to treat cancer patients recovering from chemotherapy or radiation therapy. Moreover, Applicant

has demonstrated in a rat animal model that transplanted bone-marrow derived cells and oval cells can participate in the production of hepatocytes, bile ductal cells.

Thus, given the specific teachings of the specification, one skilled in the art could, without undue experimentation, successfully stimulate liver regeneration in a subject by administration of bone marrow cells to the subject. All that is required is that the skilled artisan follow the teachings of the specification.

CONCLUSION

Entry of the foregoing remarks into the file history of the above-identified application is respectfully requested. Applicant believes that the foregoing remarks place the claims in condition for allowance. Withdrawal of all rejections and reconsideration of the claims is requested.

Respectfully submitted,

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